REMARKS

Claims 1 and 24 are all the claims pending in the application.

The body of Claim 1 has been amended to incorporate the recitations of claims 4, 6 and 8. In addition, the preamble has been amended to incorporate the preambles of claims 22 and 23, as supported in the specification, for example, in the paragraph bridging pages 20 and 21.

New claim 24 is supported at least from page 24, line 16 to page 28, line 5 of the specification.

A. Elections/Restrictions

The Examiner asserts that newly submitted claims 22-23, drawn to methods for assessment of severity and/or acuteness or assessment regarding progress of cystic fibrosis do not read on the elected species of diagnosis. Accordingly, claims 22-23 are withdrawn from further consideration pursuant to 37 CFR § 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 22-23 have been canceled.

The preamble of claims 22 and 23 have been incorporated into amended claim 1, but not the bodies of the claims. That is, the steps of claim 1 have not been amended to include the steps of claims 22 or 23. Accordingly, unity of invention is present.

B. Claim Objections

Claim 1 is objected to because in claim 1 the first instance of the abbreviation "CAP 18" should be accompanied by the full term. Claim 1 is also objected to as not using proper antecedent basis by reciting said "CAP 18" in light of the prior reference to "native CAP 18."

This objection is overcome by amending claim 1 to include the definition of CAP 18 at the first occurrence of the abbreviation and to modify "CAP 18" with the word "native," all occurrences.

C. Claim Rejections - 35 U.S.C. § 112, first paragraph - new matter

Claims 1, 4-8, 11-15, and 21 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

The Examiner asserts that there is no written description of the step of:

1. genotypically or phenotypically confirming the diagnosis or the determination of the presence or absence of risk or assessment of the level of the risk.

This rejection is overcome by amending claim 1 to delete this recitation. Furthermore, since the claim expressly states that the diagnosis is only a "possible" diagnosis, the method is more like a screening procedure to identify candidates for further testing. Therefore, the claim is enabled without a confirming step.

D. Claim Rejections - 35 U.S.C. § 112, second paragraph

Claims 1, 4-8, and 11-15 remain rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner states that amending claim 1 to recite "native CAP 18" does not overcome the rejection because the specification merely indicates that the adjective "native" indicates that the protein is "non-mutated" (page 7, penultimate paragraph). Therefore, according to the Examiner, the protein allegedly could be any of the 170-amino acid protein, the 37-amino acid protein, or the 140-amino acid protein, all designated in the literature as "CAP 18."

This rejection is overcome by amending claim 1 to recite that CAP 18 is native cationic antimicrobial protein of 18 kDa. In this respect, "native CAP18" is well known to one of ordinary skill in the art. As is clear from the following references, native CAP 18 consists of 170 amino acids which comprise a 30 amino acid signal peptide and a 140 amino acid protein (Reference 1, Fig.2 and Reference 2, columns 21-22 "7. Cloning of Human CAP18", SEQ ID NO:2) and LL-37 is the C-terminus 37 amino acids in CAP 18 (Reference 2, SEQ ID NO:6). This is consistent with the description in the present specification of what is intended as "native CAP18" described below. Therefore, it would be readily apparent to one of ordinary skill in the art that "native CAP 18" is a protein consisting of 170 amino acids, and that the protein consisting of 140 amino acids and the peptide consisting of 37 amino acids described in the literature are produced by deletion of part of the 170 amino acid polypeptide.

Description in the present application referring to CAP 18 (page 7, 3rd and 4th full paragraphs)

> As mentioned above, CAP 18 is a protein whose amino acid sequence has already been known. For the purpose of illustration, the entire amino acid sequence of human CAP 18 is appended hereto (SEQ ID NO: 4).
>
> A naturally occurring protein may undergo substitution, deletion, insertion, transposition, or other alterations in its amino acid sequence, as a result of mutation or polymorphism of the DNA encoding the protein or intravital modification occurring after the protein has been biosynthesized. Nevertheless, some proteins are known to exhibit physiological or biological activities substantially equivalent to those of their corresponding polypeptides having no mutations. Therefore, the expression "CAP 18," which is the object of

assessment of the present invention, encompasses proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, *etc.*

References describing CAP 18

The Examiner's attention is also directed to the following references. For the Examiner's convenience, a copy of reference 1 is submitted herewith.

1. Larrick, *et al.,* Infection and Immunity, Apr. 1995, Vol.63, No.4, p.1291-1297.

In the right column, "RESULT" on page 1292, there is the following description:

"Identification of human CAP 18.

The human CAP 18 cDNA was identified and sequenced as described in Materials and Methods (see Fig. 1 and 2), Translation of the cDNA revealed a protein with a conventional 30-amino-acid signal sequence."

2. Larrick, *et al.,* US Patent No. 5,615,675

3. http://shop.innovagen.com/peptide.php?code=SP-LL37

Name LL-37

Sequence

LLGDFFRKSKEKIGKEFKRI V QRIKDFLRNLV PRTES

3-letter-code

Leu - Leu - Gly - Asp - Phe - Phe - Arg - Lys - Ser - Lys - G1u-Lys-Ile-Gly-Lys-Glu-Phe-Lys-Arg-Ile-Val-Gln-Arg-Ile-Lys-Asp-Phe-Leu-Arg-Asn-Leu-Val-Pro - Arg - Thr - Glu - Ser

Description: The cathelicidin anti-microbial peptide LL-37 corresponds to amino acids 134-170 of the human cationic antimicrobial protein 18 (hCAP 18).

As described above, it is described that LL37 is C terminus peptide in 170 amino acids.

4. Wikipedia (R)

http:/len.wikipedia.org/wiki/Cathelicid

in Cathelicidin

(5)NCEI (Protein)

http:/lwww.ncbi.nlm.nih. gov/entrez/viewer.fcgi?db=protein&id=1706745

LOCUS P49913 170 as

Cathelicidin antimicrobial peptide precursor (18 kDa cationic antimicrobial protein) (CAP-18) (hCAP-18) [Contains: Antibacterial protein FALL-39 (FALL-39 peptide antibiotic); Antibacterial protein LL-37].

http: //www.ncbi.n1m.nih.govlentrezJv_ie_wer.fcgi ?db=protein&id=26517234

LOCUS AAN78318 170 as

http: //www.ncbi.n1m.nih. sovlen *trezJviewer,* fcgi?db=protein&id=1322244

LOCUS AAC02634 170 as

DEFINITION antimicrobial protein CAP 18 precursor [Homo sapiens].

REFERENCE 1 (residues 1 to 170)

AUTHORS Larrick,J.W., I-Iirata,M., Balint,R.F., Lee,J., Zhong,J. and Wright,S.C.

TITLE Human CAP 18: a novel antimicrobial lipopolysaccharide-binding protein

JOURNAL Infect. Irnmun. 63 (4), 1291-1297 (1995)

PUBMED 7890387

In view of the above remarks and evidence, the Examiner is requested, respectfully, to reconsider and remove this rejection.

E. Claim Rejections - 35 U.S.C. § 102

Claims 1, 4-7, 11-14, and 21 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Bals et al. ("Salt-Independent Abnormality of Antimicrobial Activity in Cystic Fibrosis Airway Surface Fluid" *Am. J. Respir. Cell Mol. Biol.* **25** (2001), p. 21-25) and in light of the evidence of iHOP (Information Hyperlinked over Proteins - data for CAMP, cathelicidin antimicrobial peptide, p. 1, downloaded from http://www.ihop-net.org/UniPub/iHOP/gs/86912.html on 01/04/2007). The Examiner asserts that Bals et al. teaches every step of the rejected claims. With respect to Applicant's arguments that Bals et al. teaches away from correlating CAP 18 level with a diagnosis of cystic fibrosis and that the prior amendments to recite a correlation step have obviated the grounds of rejection, the Examiner states that the recited correlation step is not found to further limit the scope of the claim. The Examiner asserts that the whereby clause does not require an actual step of diagnosing.

This rejection is overcome by amending claim 1 to reword the whereby clause as a positive step of diagnosing.

F. Claim Rejections - 35 U.S.C. § 103

Claims 8 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bals et al. in view of Weinberg et al. (US 6,187,536 Bl) and in light of the evidence of iHOP.

With respect to Applicant's arguments that Bals et al. teaches away from correlating CAP 18 level with a diagnosis of cystic fibrosis and that the instant amendments to recite a correlation step have obviated the grounds of rejection, the Examiner states that the recited correlation step is not found to further limit the scope of the claim. Therefore, the Examiner concludes that

whether Bals et al. teaches away from diagnosis of cystic fibrosis based on measurement of CAP 18 is moot.

This rejection is overcome by amending claim 1 to positively recite a diagnosis of possible cystic fibrosis based on CAP 18 levels.

Furthermore, in the paragraph: "Determination of Peptide Concentrations by Dot-Blot and Immunoblot Analysis" in the left column on page 22 and Fig. 4 on page 23 in Bals, there is a description of the results of a Dot-Blot of samples obtained from CF patients and control patients by bronchoscopyl using anti-serum (polyclonal antibody) against LL-37. Additionally, the first paragraph in the left column on page 24 in Bals states that "As shown in Figure 4, concentrations of antimicrobial peptides are not significantly different in ....or BALFs of CF patients (Figure 4B) as compared with control patients".

Even when LL-37 is measured by Dot-Blot, a significant difference cannot be shown. Bals does not describe the possibility of CF diagnosis at all. Since CF diagnosis in view of CAP 18 and hBD (human p-defensin) are not described in Bals, Bals only indicate the possibility that other biophylaxis factors act (or are lacking) which have not been identified. Furthermore, in Western Blotting using anti LL37 antibody, many kinds of heterogeneous analytes (free analytes in a biological sample or secreted analytes) which have at least LL37 are supposed to exist.

On the other hand, at page 27, lines 1-18 ((2) Evaluation of CF by use of BALF) the present application describes that CAP 18 level of CF patients which is measured by the method described in claim 1 is significantly higher than that of healthy humans. The description is as follows:

(2) Evaluation of CF by use of BALF

BALF samples obtained from patients suffering CF and healthy humans were employed as biological samples, and the amount of CAP 18 contained in each sample was measured through the measurement method described in (1) above. The results ("mean, ±SD") are shown below.

BALF samples from CF patients (n=23) 189.7±18.7 (μg/mL)

BALF samples from healthy humans (n=12) 120.7±24.7 (μg/mL)

p=0.036 (unpaired 2-tail t test)

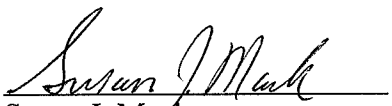
These results indicate that the CAP 18 levels of BALF samples determined for the patients suffering CF are significantly higher than those determined for healthy humans. Accordingly, when the CAP 18 level of a BALF sample of a certain individual is high, the measurement can be correlated with "CF is confirmed" or "high possibility of CF being confirmed."

Diagnosis of CF patients with significant difference is possible for the first time by using the method described in amended claim 1 (canceled claim 8). Such an effect cannot be easily expected by one of ordinary skill in the art based a disclosure in Weinberg et al. of a general sandwich type assay method.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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Date: July 28, 2008